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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,463	04/05/2001	Nobuto Yamamoto	Y1004/20017	2419

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,463	YAMAMOTO, NOBUTO	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0105*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/21/2004 has been entered.

Claims 22 and 24 are pending and being examined.

Applicant's arguments filed 10/20/2004 have been fully considered but they are not persuasive because they do not address the present rejection of claim 22 and because they do not address the new grounds of rejection of claim 24 under 35 USC § 103.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (A (U. S. Patent No. 5,177,002)) in view of Cooke (U (J Clin Invest. 1985 Dec;76(6):2420-4)), Quirk (U (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87)), Lichenstein (A (U. S. Patent No. 5,652,352)), Murphy (B (U. S. Patent No. 5,516,657)), and Luckow (V).

Yamamoto teaches a process of converting glycosylated Gc protein (Gc1 isoform) to a highly potent macrophage activating factor (GcMAF) by contacting Gc protein with immobilized

β-galactosidase and sialidase (Example 2, columns 9-10; paragraph bridging columns 2-3; column 4, full paragraph 2; paragraph bridging columns 4-5). The innermost sugar of the oligosaccharide moiety of Gc1 protein is N-acetylgalactosamine. Treatment of Gc1 protein with endo-N-acetylglucosaminidase, which results in the cleavage of the N-acetylgalactosamine, results in a molecule which cannot be then converted to macrophage activating factor (column 5, full paragraph 1). The macrophage activating factor is believed to comprise a protein in substantially pure form having substantially the amino acid sequence of human group specific component, and a terminal O-linked N-acetylgalactosamine group (column 5, full paragraph 3). The Gc protein has a molecular weight of about 52,000 (sentence bridging columns 1-2) and comprises approximately 458 amino acids, as indicated in Figures 1 and 2. The Gc protein has a molecular weight of about 52,000, comprises approximately 458 amino acids, and has three distinct domains, as evidenced by Cooke (Figure 3; page 2423, paragraph bridging left and right columns).

The Gc protein is purified from human blood (column 5, full paragraph 5).

The Gc protein is also known as "vitamin-D binding protein" (paragraph bridging columns 1-2). Yamamoto refers to Cooke for nucleotide and amino acid sequences of Gc protein (paragraph bridging columns 1-2).

Yamamoto does not teach, in the sense that Yamamoto does not anticipate, Gc protein obtained via recombinant DNA technology and its conversion to GcMAF.

The concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology. See Quirk, page 273,

last full paragraph. Material derived from E. coli may present the problem of co-purification of LPS which has endotoxin activity. See Quirk, paragraph bridging pages 273-274.

Cooke discloses a cDNA encoding the human vitamin D-binding protein (hDBP) and its nucleotide and amino acid sequence (page 2421, Figure 2). Comparison of the sequence of the hDBP mRNA and protein to existing protein and nucleic acid data banks demonstrates a strong and highly characteristic homology of the hDBP with human albumin (hALB) and human alpha-fetoprotein (hAFP). Based upon this structural comparison, Cooke establishes that DBP is a member of the ALB and AFP gene family. See the Abstract. Cooke's sequence represents the Gc1 allele (page 2424, left column).

Lichenstein discloses that the human serum proteins albumin (ALB), α-feta-protein (AFP) and vitamin D binding protein (VDB) are known to be members of a multigene ALB family. All three proteins are found in serum. See column 1, lines 10-15. Lichenstein discloses human afamin (AFM). It shares strong similarity to albumin family members and has the characteristic pattern of disulfide bonds observed in this family. In addition, the gene maps to chromosome 4 as do other members of the albumin gene family. Thus, AFM is the fourth member of the albumin family of proteins. AFM cDNA was stably transfected into Chinese hamster ovary cells and recombinant protein (rAFM) was purified from conditioned medium. column 1, lines 45-65. Host cells from mammals, prokaryotes, fungi, yeast, insects and the like are used for the recombinant expression of AFM (column 13, lines 52-55).

Murphy provides Baculovirus vectors to express recombinant proteins during Baculovirus infection. One advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic

and are antigenically and/or biologically active. In addition, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems. Although mammalian expression systems result in the production of fully modified, functional protein, yields are often low. E. coli systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state. See column 1, lines 40-52. The list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (column 6, full paragraph 3).

Luckow discloses that baculovirus vectors have become widely used to direct the expression of foreign genes. The recombinant proteins are antigenically, immunogenically, and functionally similar to their authentic counterparts (page 51, full paragraph 1). Luckow discloses recombinant baculoviruses and baculovirus vectors (pages 55-66). Luckow discloses that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (page 74, full paragraphs 2-3). Expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (page 83, last full paragraph). PCR can also be used to facilitate the engineering of foreign genes for insertion into baculovirus transfer vectors (page 55, full paragraph 1, last sentence).

Cooke, Quirk, Lichenstein, Murphy, and Luckow do not teach, in the sense that Cooke, Quirk, Lichenstein, Murphy, and Luckow do not anticipate, Gc protein obtained via recombinant DNA technology and its conversion to GcMAF.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to purify a Gc1 isoform from blood, contact the purified Gc1 isoform in

vitro with immobilized β-galactosidase and sialidase, and obtain GcMAF, as taught by Yamamoto, and to modify that teaching by obtaining the Gc protein via recombinant DNA technology, i.e., cloning a Gc1 isoform into a baculovirus vector and expressing the cloned Gc1 isoform, using the teachings of Cooke, Quirk, Lichenstein, Murphy, and Luckow, with a reasonable expectation of success.

One of ordinary skill in the art would be motivated to make this modification because the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology, material derived from E. coli may present the problem of co-purification of LPS which has endotoxin activity, E. coli systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state, Gc protein (vitamin D binding protein) is a ALB family member, host cells from insects can used for the recombinant expression of an ALB family member, foreign genes for human blood factors may be inserted into Baculovirus vectors, one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems, although mammalian expression systems result in the production of fully modified, functional protein, yields are often low, recombinant proteins expressed in baculovirus systems are antigenically, immunogenically, and functionally similar to their authentic counterparts, O-linked glycosylation is known to occur on foreign proteins expressed in insect cells, and expression of foreign genes

by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to PCR-amplify Cooke's cDNA encoding the human vitamin D-binding protein, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to facilitate the engineering of the foreign gene encoding the human vitamin D-binding protein for insertion into baculovirus transfer vectors.

The invention is prima facie obvious over the prior art.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (A (U. S. Patent No. 5,177,002)) in view of Cooke (U (J Clin Invest. 1985 Dec;76(6):2420-4)), Quirk (U (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87)), Lichenstein (A (U. S. Patent No. 5,652,352)), Murphy (B (U. S. Patent No. 5,516,657)), and Luckow (V) as applied to claim 22 above, and further in view of Sambrook (U).

Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow teach a process for producing GcMAFc comprising cloning a PCR-amplified Gc1 isoform into a baculovirus vector, expressing the cloned Gc1 isoform, contacting the expressed Gc1 isoform with immobilized β-galactosidase and sialidase, and obtaining the GcMAFc, as discussed above. Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow do not teach sequencing the cloned Gc1 isoform.

Sambrook teaches that the sequence of an individual DNA molecule cloned from a PCR amplified pool is unreliable. Any sequence obtained in this manner should be confirmed by sequencing. Page 14.5, last full paragraph. Sambrook does not teach a process for producing GcMAFc comprising cloning a PCR-amplified Gc1 isoform into a baculovirus vector, expressing the cloned Gc1 isoform, contacting the expressed Gc1 isoform with immobilized β-galactosidase and sialidase, and obtaining the GcMAFc.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to clone a PCR-amplified Gc1 isoform into a baculovirus vector, express the cloned Gc1 isoform, contact the expressed Gc1 isoform with immobilized β-galactosidase and sialidase, and obtain the GcMAFc, as taught by Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow, and to modify that teaching by sequencing the cloned Gc1 isoform with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the sequence of an individual DNA molecule cloned from a PCR amplified pool is unreliable. Any sequence obtained in this manner should be confirmed by sequencing. Confirmation of the sequence would confirm that the sequence of the cloned Gc1 isoform is the sequence of Cooke's Gc1 isoform. Cooke's Gc1 isoform is a "wild type Gc1 isoform" in the absence of evidence to the contrary. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, claimed properties or functions are presumed to be inherent, and a prima facie case of either anticipation or obviousness has been established. Therefore, the GcMAFc obtained is "functional."

The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Support for the limitation "sequencing the cloned Gc1 isoform, thereby ... wild type Gc1 isoform;" cannot be found in the originally filed disclosure, which raises the issue of new matter.

Applicant argues that no new matter is added because the present specification discloses the amino acid sequence and cDNA sequence of the Gc protein and that one of ordinary skill in the art would be able to confirm the sequence by utilizing standard sequencing technology. Applicant's arguments have been fully considered but they are not persuasive. Although standard sequencing technology may have enabled the sequencing of a cloned Gc1 isoform and comparing the sequence obtained with the presently disclosed sequence at the time of Applicant's invention, the present specification does not describe this procedure. Furthermore, the written description provision of 35 USC 112 is severable from its enablement provision. Therefore, this newly included procedure in the claimed invention raises the issue of new matter.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300 CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MARCH 1, 2005